Apoptotic colonopathy under immunosuppression: Mycophenolate-related effects and beyond

Weber, Achim ; Marques-Maggio, Ewerton

Abstract: Background/Aims: Diarrhea developing in patients under immunosuppression has a variety of underlying causes. A broad spectrum of histological findings can be found in intestinal biopsies taken for the diagnostic workup of diarrhea including a pathologically increased proportion of epithelial cell apoptosis in the colon, for which the descriptive term 'apoptotic colonopathy' was coined. In recent years, the immunosuppressive drug mycophenolate (mycophenolic acid, MPA) has been identified as a prototypical cause of apoptotic colonopathy, but other conditions may show similar or overlapping histological pictures. Methods: Cases of likely or possible MPA colonopathy (n = 18) were retrospectively identified from the archive files. Clinical information on patient history, clinical presentation and endoscopic findings were recorded. All cases were routinely processed, i.e. stained by hematoxylin and eosin (HE) stain, optionally supplemented by special histochemical and immune stains. Results and Conclusion: Histopathological hallmarks of MPA treatment-related changes in the colon mucosa are reviewed with respect to the major histopathological differential diagnoses including normal and near-normal findings, infectious diseases, graft-versus-host disease and inflammatory bowel diseases. Furthermore, the challenge of multiple concomitant pathologies while on MPA treatment, in particular infectious diseases, is discussed, and some open questions concerning the effects of MPA on colon pathology are pointed out.

DOI: https://doi.org/10.1159/000350758

Pathobiology

Pathobiology 2013;80:282–288
DOI: 10.1159/000350758

Published online: September 2, 2013

Apoptotic Colonopathy under Immunosuppression: Mycophenolate-Related Effects and Beyond

Achim Weber Ewerton Marques-Maggio

Institute of Surgical Pathology, University of Zurich, Zurich, Switzerland

Key Words
Apoptotic colonopathy · Mycophenolate · Infectious disease

Abstract
Background/Aims: Diarrhea developing in patients under immunosuppression has a variety of underlying causes. A broad spectrum of histological findings can be found in intestinal biopsies taken for the diagnostic workup of diarrhea including a pathologically increased proportion of epithelial cell apoptosis in the colon, for which the descriptive term 'apoptotic colonopathy' was coined. In recent years, the immunosuppressive drug mycophenolate (mycophenolic acid, MPA) has been identified as a prototypical cause of apoptotic colonopathy, but other conditions may show similar or overlapping histological pictures. ***Methods:*** Cases of likely or possible MPA colonopathy (n = 18) were retrospectively identified from the archive files. Clinical information on patient history, clinical presentation and endoscopic findings were recorded. All cases were routinely processed, i.e. stained by hematoxylin and eosin (HE) stain, optionally supplemented by special histochemical and immune stains. ***Results and Conclusion:*** Histopathological hallmarks of MPA treatment-related changes in the colon mucosa are reviewed with respect to the major histopathological differential diagnoses including normal and near-normal findings, infectious diseases, graft-versus-host disease and inflammatory bowel diseases. Furthermore, the challenge of multiple concomitant pathologies while on MPA treatment, in particular infectious diseases, is discussed, and some open questions concerning the effects of MPA on colon pathology are pointed out.

Introduction

Diarrhea is a clinical symptom reflecting abnormalities in the gastrointestinal tract of a variety of different diseases. Diarrhea developing in immunocompromised individuals differs from diarrhea developing in immunocompetent individuals with respect to the spectrum of underlying causes, pathophysiological mechanisms, clinical presentation and histopathological findings. Integrity of the intestinal mucosa is one of the many factors required for a normal bowel function. The intestinal epithelial layer at the mucosal surface has a barrier function which is crucial for mucosal integrity. The intestinal epithelium is a dynamic compartment and is subject to permanent turnover and regeneration in case of injury. Intestinal epithelial cells (EC) have a high turnover rate and are estimated to be replaced every 3–5 days. Besides physiological shedding of intestinal EC into the bowel lumen, intestinal EC may be lost as the result of damage to the epithelium. A morphological correlate of such damage is the occurrence of apoptosis in intestinal EC.

KARGER

E-Mail karger@karger.com
www.karger.com/pat

1015–2008/13/0806–0282$38.00/0

Achim Weber, MD
Institute for Surgical Pathology, University Hospital Zurich
Schmelzbergstrasse 12
CH–8091 Zürich (Switzerland)
E-Mail achim.weber@usz.ch

Table 1. Histological findings in colon biopsies of patients with (suspected) MPA colonopathy

No.	Age	Sex	Med hx	Clinical presentation	Biopsy information	Histological findings	Additional findings	Causality[a]
1	60	M	K-TPL	watery diarrhea	colon	ACE, CDC, CAD, inflammation	erosions	++
2	70	M	K-TPL	diarrhea	colon	ACE, CAD, inflammation		++
3	75	M	K-TPL	diarrhea	colon frame	ACE, CAD, inflammation		++
4	58	M	K-TPL	diarrhea	colon frame	ACE	IEL	+
5	40	M	K-TPL	diarrhea	colon frame	ACE, CDC, CAD, inflammation		++
6	45	F	K/P-TPL	diarrhea	colon frame	ACE, CAD	kayexalate	+
7	48	M	K-TPL	diarrhea	colon steps	ACE, CDC, CAD, inflammation, EOS		++
8	26	F	K-TPL	diarrhea with blood	colon right and left	ACE, CAD, inflammation	mucinous granulomas	+
9	43	F	L-TPL	weight loss	colon, 45 cm	ACE, CAD, inflammation		+
10	53	M	K-TPL	diarrhea	colon	ACE, CDC, CAD, inflammation, EOS		++
11	65	M	K-TPL	diarrhea	colon, rectum	ACE, CDC, CAD, inflammation, EOS	muciphages	+
12	54	F	K-TPL	diarrhea	colon	ACE, CAD, inflammation	CMV reactivation	++
13	38	F	K-TPL	abdominal pain	colon	ACE, CAD, inflammation		+
14	64	M	K-TPL	diarrhea	colon frame	ACE, CAD, inflammation, EOS		++
15	54	F	K-TPL	diarrhea, weight loss	colon	ACE, CAD, inflammation	same patient as No. 12	+
16	11	F	SLE	diarrhea	cecum, rectum	ACE, CDC, CAD, inflammation, EOS	thrombotic microangiopathy	+
17	38	F	K-TPL	abdominal pain, weight loss	colon	ACE, CDC, CAD, inflammation	same patient as No. 13	+
18	53	F	K-TPL	diarrhea	colon	ACE, CDC, CAD, inflammation, erosions	CMV infection, tapeworm	+

ACE = Apoptosis of crypt epithelium; CAD = crypt architectural disarray; CDC = cystically dilated crypts; EOS = eosinophils; IEL = intraepithelial lymphocytosis; K/P-TPL = combined kidney and pancreas transplantation; K-TPL = kidney transplantation; SLE = systemic lupus erythematosus; Med hx = medical history.

[a] Changes due to MPA are possible (+) or likely (++), when regarding the symptoms and histological findings.

Materials and Methods

For this study, cases of likely or possible mycophenolate (mycophenolic acid, MPA) colonopathy were retrospectively identified from the files of the Institute of Surgical Pathology, University Hospital Zurich, for the period 2009–2012. Clinical information on patient history, clinical presentation and endoscopic findings were recorded, when available, from clinical information. All cases were routinely processed, i.e. stained by hematoxylin and eosin (HE) stain, optionally supplemented by special histochemical and immune stains for suspected infectious agents. Overall, we identified 18 cases of likely or possible MPA colonopathy in 16 different patients (rebiopsies in 2 cases; see table 1). The study was in line with the local ethical regulations (Reglement für den Zugriff auf Patientendaten zu Forschungszwecken; University Hospital Zurich).

Apoptosis in Normal Colonic Mucosa and Bowel Preparation Effects

As it takes more than one swallow to make a summer, it takes more than one colonic apoptosis to make a colonic pathology. A single apoptotic intestinal EC in an otherwise unremarkable colonic mucosa is not abnormal per se. In early studies performed to quantify how many apoptoses can be found in a nondiseased colonic mucosa, a threshold of 5 apoptotic bodies per 100 crypts found in an HE-stained slide has been determined [1]. When evaluating colonic biopsies, one has to be aware of histological changes resulting from the bowel preparation procedure; this includes scattered apoptosis of colonic EC [2]. For practical purposes, the finding of more than an occasional apoptotic colonic EC should be regarded as abnormal and prompt a search for an underlying condition. The histological finding of a pathologically increased number of apoptoses in the colon mucosa is coined with the generic term apoptotic colonopathy.

MPA-Induced Colonopathy

In recent years, we increasingly observed colonic biopsies taken for the clinical workup of diarrhea that revealed (among others) the finding of apoptotic colonopathy which was ultimately related to the use of the immunosuppressive drug MPA. This observation in our practice was paralleled by a growing body of literature on MPA-

related histopathological findings [3–6]. MPA is an inhibitor of inosine-5′-monophosphate dehydrogenase and blocks the de novo purine synthesis required for DNA synthesis and cell division. MPA and its prodrug mycophenolate mofetil (MMF) have several immunosuppressant actions and prevent allograft rejection by several mechanisms: proliferation of T and B lymphocytes is inhibited and cell-mediated immune responses and antibody formation are suppressed, dendritic cell maturation impaired and anti-inflammatory activity further impaired by the inhibition of interleukin (IL-1) expression together with the enhanced expression of the IL-1 receptor antagonist [7]. MPA is frequently used to prevent rejection in (solid) organ transplantations, and is available either as the prodrug MMF (CellCept®, Roche Pharma AG, Reinach, Switzerland) or the salt mycophenolate sodium (Myfortic®, Novartis Pharma AG, Stein, Switzerland), differing mostly with respect to a more gastric or enteric absorption, respectively [8].

Among other adverse effects, MPA may also cause damage to the gastrointestinal tract [9]. Typical clinical presentations of MPA-related gastrointestinal toxicity include afebrile, watery diarrhea with mostly unremarkable or mild endoscopy findings. The entire gastrointestinal tract including the upper part can be affected by MPA toxicity [3], and macroscopic features may include ulcers and erosions throughout the entire gut. The epithelial or glandular compartment is the main target of MPA-related toxicity. The predominant patterns of injury are an acute inflammatory pattern and/or an apoptotic pattern. Major histopathological findings comprise a picture resembling self-limited colitis, an inflammatory bowel disease (IBD)-like picture and a graft-versus-host disease (GvHD)-like picture [4, 6, 10]. Typical histological features include a (mostly mild) crypt architectural disarray, colonic crypt atrophy and dropout which may result in an IBD-like pattern over time (fig. 1a, left), a paucity of inflammatory cells in the lamina propria ('empty lamina propria appearance'), atrophy of the epithelial lining cells with typical dilated crypts containing an attenuated epithelial lining and cellular debris in their lumen (fig. 1a, middle) and a notably increased number of crypt cell apoptoses (fig. 1a, right). As illustrated in figure 1a, the different histopathological key findings are best evaluated on low-power view (architecture, left), medium-power view (epithelial changes, middle) and high-power view (apoptosis, right), respectively. Whereas none of the above-mentioned findings is specific for MPA, the simultaneous observation of a mixed pattern of injury (architectural distortion, increased number of crypt cell apoptosis, epithelial changes with cystically dilated crypts) is characteristic for MPA toxicity [6, 10–12]. Variably encountered additional findings are an increased number of eosinophils in the lamina propria and a (relatively) increased number of neuroendocrine cells which seem to be less prone to undergo apoptosis.

In contrast to the early years of MPA use, with an increased awareness of MPA toxicity deriving from clinical sites, information on MPA treatment is nowadays frequently given. The above-listed histopathological findings – especially when a combination of the several patterns is found – are so characteristic of MPA toxicity that this must be mentioned with the differential diagnoses in the pathology report, even when corresponding clinical information is lacking. In our experience, in such cases, communication with clinical partners regarding specific questions on MPA treatment can be helpful, in many instances leading to the diagnosis.

Differential Diagnoses

Unfortunately, even when the full spectrum of changes listed is present, the above-listed histopathological findings are not restricted to cases of MPA toxicity. The most relevant differential diagnoses are listed in table 2 with respect to features useful for differential diagnostic considerations. As outlined, MPA toxicity can present with histological pictures resembling self-limited infectious colitis, IBD and/or GvHD, respectively; these are thus obviously among the differential diagnoses. In daily practice, IBD is not a major differential diagnosis, as medical history, clinical presentation and endoscopic findings of IBD patients are mostly different from patients with MPA colonopathy. Histopathologically, MPA colonopathy and IBD may both have architectural disarray. However, IBD typically has an increased inflammatory infiltrate in the lamina propria which is in contrast to the paucicellular ('empty-appearing') lamina propria in MPA colonopathy. Furthermore, IBD cases tend to have more features of chronicity, and metaplasia (mucinous or pyloric-gland type) or granulomas can be found which are typically not seen in MPA colonopathy.

In contrast, infectious colitis is a relevant differential diagnosis. Increased apoptosis of the crypt epithelium is a feature of infections caused by a variety of agents including bacterial infections, especially the toxin-producing ones, and in particular viral infections caused by human cytomegalovirus (CMV) and adenovirus, but also protozoal infections, especially *Cryptosporidium*. Patients un-

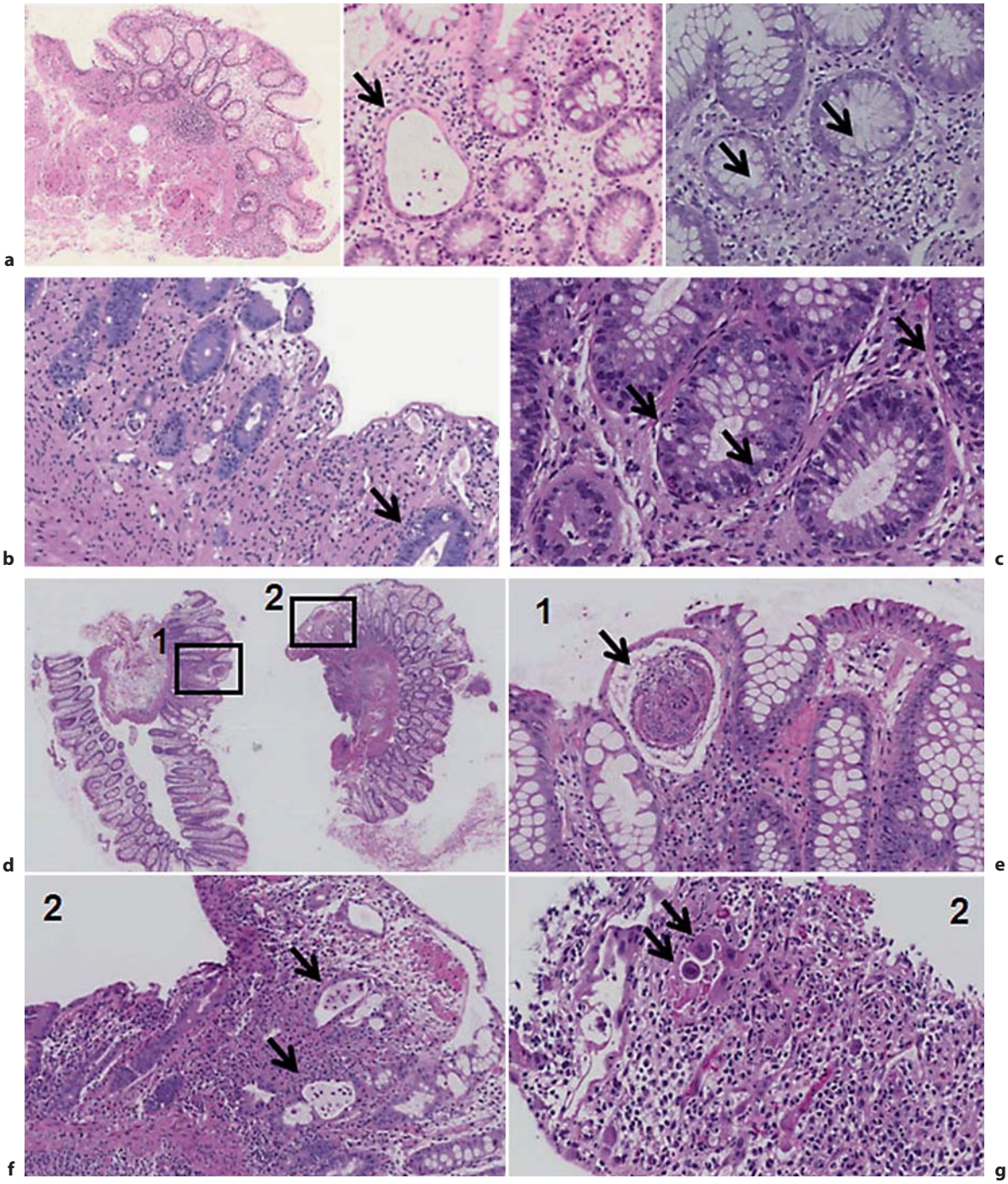

Fig. 1. a Histological hallmarks of MPA-related colonopathy. Left: IBD-like pattern with architectural disarray and empty appearing lamina propria. Middle: atrophic cystically dilated crypts (arrow) with luminal cellular debris. Right: multiple apoptosis of basal crypt epithelium cells (arrows). Magnification ×2.5, ×10 and ×10, respectively. **b** Colonic biopsy with GvHD revealing denudation of the surface epithelium, spare infiltrate of cells in the lamina propria, and multiple apoptosis of basal crypt epithelium cells (arrow). Magnification ×5. **c** Colonic biopsy of a case of AIDS-related colonopathy revealing also multiple apoptosis of basal crypt epithelium cells (arrows). Magnification ×20. **d–g** Colonic biopsy of a patient developing diarrhea while on treatment revealing multiple pathologies including changes consistent with MPA-induced effects. **d** Low-power view reveals mild architectural disarray: framed areas 1 and 2 have additional distinct findings. Magnification ×0.38. **e** High-power view of area 1 in **d** with a section of the dwarf tapeworm *(Hymenolepis nana)*. Magnification ×10. **f**, **g** High-power views of area 2 in **d** revealing active colitis with erosions, cystically dilated crypts and multiple EC with both nuclear and cytoplasmic inclusions indicating CMV infection. Magnification ×5 and ×10, respectively.

Table 2. Histological findings in MPA colonopathy with respect to its differential diagnoses

Condition	Histopathological findings				Diagnostic clues	
	ACE	CAD	CDC	EOS	histopathology	history/clinical findings/endoscopy
MPA colonopathy	++	+	++	+	paucicellular ('empty-appearing') lamina propria	history of TPL and MPA intake, watery diarrhea, mostly unremarkable endoscopy
Bowel preparation effects	+	–	–	–	apoptosis and proliferation in crypt epithelium, may show focal active colitis, preserved architecture	mostly unremarkable endoscopy or small aphthoid lesions more in distal colon/rectum
GvHD	++	+	–	–	mucosal damage, mucosa might be totally denuded; possible CAD in late stage	history of bone marrow, stem-cell or (rarely) solid organ transplantation; signs of GvHD in liver or skin; triad of diarrhea, nausea and vomiting; variable endoscopic findings from normal-appearing to severely damaged/denuded mucosa
IBD	+	++	–	+	increase of lamina propria inflammatory cells; active colitis, intense neutrophilic activity; chronic and ongoing mucosal injury; metaplasia (mucinous or pyloric gland type), granulomas; (post-) inflammatory polyps	history of IBD, abdominal pain, fever; variable mucous or bloody diarrhea; significant mucosal inflammation; signs of long-standing disease
Acute (self-limited) infectious colitis	+	–	–	–	focal or diffuse active (neutrophilic) colitis including cryptitis and crypt abscesses with a background of preserved crypt architecture; variable surface damage and erosions; viral cytopathic effects and special stains including immune stains	fever; abdominal pain; mucosa with erythema, erosions and variable hemorrhage on endoscopy
AIDS-related (entero-) colonopathy	++	–	–	–	increased number of apoptoses and decreased number of mitotic figures in relation to mucosal injury; changes more prominent in small-bowel preserved crypt architecture	known HIV infection; low CD4 cell counts; exclusion of infectious agents; mostly unremarkable endoscopy
Autoimmune enterocolitis	++	+	–	–	villous atrophy; lack of goblet and Paneth (and neuroendocrine) cells; lymphocyte-mediated damage of preferentially basal parts of crypts (but not surface epithelium); increase of lamina propria inflammatory cells	very rare disorder with childhood (onset in first year of life) and adult forms; diarrhea and weight loss; associated with other autoimmune diseases; antienterocyte and anti-goblet-cell autoantibodies
Common variable immunodeficiency	++	–	–	–	decreased count of mucosal plasma cells; GvHD-, IBD-, and lymphocytic colitis-like patterns possible in colon; sprue-like pattern with villous atrophy and also nodular lymphoid hyperplasia and chronic giardiasis in small bowel	gastrointestinal symptoms (diarrhea and malabsorption) associated with sinopulmonary infections

– = Not a typical finding; + = a possible finding; ++ = a typical finding; ACE = apoptosis of crypt epithelium; CAD = crypt architectural disarray; CDC = cystically dilated crypts; EOS = eosinophils; TPL = transplantation.

der immunosuppression, including that resulting from MPA treatment, are naturally at a higher risk for developing opportunistic infections. Consequently, even in cases with features suggesting MPA-related changes like increased apoptosis of the crypt epithelium, the presence of concomitant infections must be determined, and a low threshold for further workup including more levels, specific and immune stains should be given.

GvHD [13] is probably the condition which shares the most histopathological features with MPA-related colonopathy to a degree that a GvHD-like pattern is regarded as a characteristic feature of MPA-related colonopathy. Both conditions reveal a predominantly inflammatory injury pattern affecting the epithelial compartment. Apoptosis of the crypt epithelium is a hallmark of both as well as a paucity of lamina propria inflammatory cells. GvHD may progress to a condition with marked crypt distortion resembling IBD, similar to how MPA-related colonopathy does. Although on the one hand, MPA-related colonopathy often shows cystically dilated crypts (fig. 1a, middle panel) which GvHD usually does not, and on the other hand, GvHD can have a partially or totally denuded mucosa (fig. 1a) which is not a typical MPA effect, both conditions may, in fact, look identical and can thus not be distinguished from each other purely on the basis of histology. Taking into account the clinical setting, with a history of hematopoietic cell transplantation (in rare cases, solid organ transplantation) and a clinical pre-

sentation of skin and liver affection, usually gives direction to the diagnosis of GvHD. However, if patients in the right setting for GvHD also have a history of MPA treatment, a distinction based purely on histology might be impossible and so has to be made clinically.

Other conditions with impaired or modulated immune response which have apoptotic colonopathy as a histopathological feature are autoimmune enterocolitis, common variable immunodeficiency and AIDS-related colonopathy (fig. 1c, usually observed only in patients with very low T cell counts, nowadays rarely observed in resource-rich countries due to the implementation of combination antiretroviral therapy to decrease HIV replication and restore immune status). Usually, the clinical setting is different and is known, thus rarely implicating these conditions as differential diagnoses to MPA effects. Moreover, specific or characteristic histopathological findings pointing to the underlying disease are a decreased count of mucosal plasma cells in common variable immunodeficiency [14] and a lack of goblet cells or Paneth cells in autoimmune enterocolitis [15]. Drugs, other than bowel preparations and MPA, which have been reported to lead to increased epithelial apoptosis are nonsteroidal anti-inflammatory drugs, anthraquinone laxatives [16] and chemotherapeutic agents, especially 5-FU [1, 5].

MPA-Induced Colonopathy with Multiple Pathologies

Patients taking immunosuppressive drugs are at higher risk to develop (opportunistic) infections. After hematopoietic cell transplantation, patients are at risk for GvHD. Therefore, patients on MPA treatment per se who develop diarrhea likely have a higher probability of having more than one of the above-discussed conditions. We have observed several cases in which patients on MPA treatment revealed dual or even multiple pathologies. The case of a 53-year-old female, who developed diarrhea while on MPA treatment for renal transplantation, illustrates such a scenario (fig. 1d–g). Besides histological findings consistent with MPA effects like mild architectural disarray (fig. 1d) and an increased number of crypt apoptosis, a low-power view showed areas with distinct findings already suggesting additional pathologies. A high-power view then revealed the presence of tapeworm scolices at multiple sites of the mucosa (fig. 1d, inset 1) which were identified as the dwarf tapeworm *(Hymenolepis nana)*. Other areas revealed active colitis with erosions, cystically dilated crypts and multiple EC with both nuclear and cytoplasmic inclusions (fig. 1d, inset 2) leading to the diagnosis of CMV infection. In line with our observations, in a recently published study on MPA-associated colitis, Lee et al. [11] describe dual pathology in 3 of 7 cases, 2 of which were with concomitant CMV infection. Their findings and our own observations support the notion that patients on MPA treatment do indeed have a higher risk of developing dual or multiple pathologies. Therefore, when evaluating the colonic biopsies of such patients, pathologists must be aware that the histological picture of MPA effects overlaps with that of other conditions. This calls for an active and thorough search for additional diagnoses beyond these effects.

MPA-Induced Colonopathy: Perspectives and Unanswered Questions

Despite the growing body of literature in recent years and the fact that clinicians and pathologists nowadays are aware of and familiar with the effects of MPA on the gastrointestinal tract, our knowledge is mostly based on retrospective observational and correlative studies, and several fundamental questions still remain. These include points to be addressed from a basic research as well as a clinicopathological perspective. (1) Do the histopathological findings found in association with MPA treatment [3, 4, 6, 10] correlate with the clinical symptoms, in particular diarrhea? The current concept is based on this assumption, but there are no data on the frequency of MPA-typical histopathological changes in patients not suffering from diarrhea. (2) What are the dynamics of histopathological changes and clinical symptoms in relation to MPA treatment with respect to occurrence, persistence and reversibility? (3) Are there drugs other than MPA which can cause the same spectrum of histopathological changes? We have seen, sporadically, colonic biopsies with histopathological patterns virtually identical to those of the MPA effects in our own practice [unpubl. observation], suggesting that these findings probably reflect a stereotypical final pathway of several insults rather than an MPA-specific pattern. (4) To what extent do MPA effects and IBD share pathophysiological mechanisms? The big question is: Does long-term treatment with MPA come with an increased risk for cancer development going beyond the risk attributable to immunosuppression? This is conceivable, taking into account our own observation that a persistently elevated apoptosis rate may, on its own, cause cancer in tissues with the capacity for repair [17].

Conclusions

In recent years, MPA treatment has been identified as an underlying cause of apoptotic colonopathy, along with the clinical presentation of diarrhea. Characteristic histopathological findings overlap with infectious colitis, IBD and GvHD. In daily practice, it is important to recognize these features and to consider MPA toxicity, but also to not overlook concomitant pathologies like infectious diseases, to which patients on MPA treatment are prone. There are important questions relating to the effects of MPA on the gastrointestinal tract that remain unanswered. It would be pertinent to address the causal relation and specificity of histopathological findings, the clinical symptoms (in particular, diarrhea) and the question of long-term treatment.

References

1 Lee FD: Importance of apoptosis in the histopathology of drug related lesions in the large intestine. J Clin Pathol 1993;46:118–122.
2 Driman DK, Preiksaitis HG: Colorectal inflammation and increased cell proliferation associated with oral sodium phosphate bowel preparation solution. Hum Pathol 1998;29:972–978.
3 Nguyen T, Park JY, Scudiere JR, Montgomery E: Mycophenolic acid (Cellcept® and Myofortic®) induced injury of the upper GI tract. Am J Surg Pathol 2009;33:1355–1363.
4 Papadimitriou JC, Cangro CB, Lustberg A, Khaled A, Nogueira J, Wiland A, Ramos E, Klassen DK, Drachenberg CB: Histologic features of mycophenolate mofetil-related colitis: a graft-versus-host disease-like pattern. Int J Surg Pathol 2003;11:295–302.
5 Parfitt JR, Driman DK: Pathological effects of drugs on the gastrointestinal tract: a review. Hum Pathol 2007;38:527–536.
6 Selbst MK, Ahrens WA, Robert ME, Friedman A, Proctor DD, Jain D: Spectrum of histologic changes in colonic biopsies in patients treated with mycophenolate mofetil. Mod Pathol 2009;22:737–743.
7 Allison AC, Eugui EM: Mechanisms of action of mycophenolate mofetil in preventing acute and chronic allograft rejection. Transplantation 2005;80:S181–S190.
8 Behrend M, Braun F: Enteric-coated mycophenolate sodium: tolerability profile compared with mycophenolate mofetil. Drugs 2005;65:1037–1050.
9 Behrend M: Adverse gastrointestinal effects of mycophenolate mofetil: aetiology, incidence and management. Drug Saf 2001;24:645–663.
10 Parfitt JR, Jayakumar S, Driman DK: Mycophenolate mofetil-related gastrointestinal mucosal injury: variable injury patterns, including graft-versus-host disease-like changes. Am J Surg Pathol 2008;32:1367–1372.
11 Lee S, de Boer WB, Subramaniam K, Kumarasinghe MP: Pointers and pitfalls of mycophenolate-associated colitis. J Clin Pathol 2012, E-pub ahead of print.
12 Dalle IJ, Maes BD, Geboes KP, Lemahieu W, Geboes K: Crohn's-like changes in the colon due to mycophenolate? Colorectal Dis 2005;7:27–34.
13 Shulman HM, Kleiner D, Lee SJ, Morton T, Pavletic SZ, Farmer E, Moresi JM, Greenson J, Janin A, Martin PJ, McDonald G, Flowers ME, Turner M, Atkinson J, Lefkowitch J, Washington MK, Prieto VG, Kim SK, Argenyi Z, Diwan AH, Rashid A, Hiatt K, Couriel D, Schultz K, Hymes S, Vogelsang GB: Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: II. Pathology Working Group report. Biol Blood Marrow Transplant 2006;12:31–47.
14 Daniels JA, Lederman HM, Maitra A, Montgomery EA: Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol 2007;31:1800–1812.
15 Akram S, Murray JA, Pardi DS, Alexander GL, Schaffner JA, Russo PA, Abraham SC: Adult autoimmune enteropathy: Mayo Clinic Rochester experience. Clin Gastroenterol Hepatol 2007;5:1282–1290.
16 Byers RJ, Marsh P, Parkinson D, Haboubi NY: *Melanosis coli* is associated with an increase in colonic epithelial apoptosis and not with laxative use. Histopathology 1997;30:160–164.
17 Weber A, Boger R, Vick B, Urbanik T, Haybaeck J, Zoller S, Teufel A, Krammer PH, Opferman JT, Galle PR, Schuchmann M, Heikenwalder M, Schulze-Bergkamen H: Hepatocyte-specific deletion of the antiapoptotic protein myeloid cell leukemia-1 triggers proliferation and hepatocarcinogenesis in mice. Hepatology 2010;51:1226–1236.